The Next Top Models

Extreme Farming

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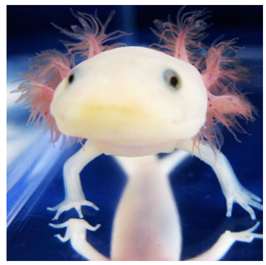
With the advent of global warming and climate change, more frequent episodes of extreme weather are predicted. That will dramatically affect food security. In addition, there will soon be more people, more meat diets, and less land for crops. Yet, food production needs to be doubled to feed the growing population by 2050. Big improvements in crop productivity under harsh environments will be required.

Model plants like Arabidopsis and rice have already paved the way to many genetic improvements in crops. Unfortunately, these model plants have not evolved to thrive in extreme environments. Some Arabidopsis relatives, specifically *Thellungiella sp.*, can instead serve as model systems for understanding how plants cope with high salinity, extreme cold, and water shortage. Besides being capable of resisting extreme environments, these small plants (with their genomes sequenced) have short life cycles, produce large numbers of seeds, and can be genetically transformed easily in large numbers. Studies on their salt tolerance revealed that these plants appear to take advantage of pre-primed stress response genes and pathways present but less effective in glycophytes, such as Arabidopsis and rice. Future work on these extremophile plants promises to elucidate strategies plants use to adapt to extreme environments and to improve crops to better cope with future harsh weather.

Axolotl Legwork



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Axolotl salamanders (*Ambystoma mexicanum*) can regenerate limbs throughout life following amputation. Their limbs are remarkably anatomically similar to human limbs, containing the full repertoire of tissues and patterned in similar ways. A vast amount of experimentation in the field of amphibian limb regeneration was conducted by some of the leading biologists of the time in previous centuries. These older experiments at a pre-molecular level are a goldmine for modern studies. From these perspectives, axolotl is an ideal model for understanding natural regeneration.

Axolotls form a transient niche-like structure called ‘‘blastema’’ to localize and multiply activated progenitor cells. We are approaching the questions of blastema formation and function with no a priori assumptions about the genes that drive these processes as the axolotl genome is enormous ($\sim$32 Gb) and largely unsequenced. Taking an a priori approach has only become feasible in the last several years with the advent of next-gen sequencing and the development of powerful new technologies for functional experimentation, such as transgenesis, viral transduction, and gene editing. Thus, this is the perfect time to be using axolotls to elucidate the mechanisms underlying the fascinating process of regeneration. The hope is that, in the future, this information will help in formulating hypotheses about why humans and other mammals have much more restricted natural regenerative abilities and eventually taking effective approaches to circumvent these limitations.

The Naked Truth

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Naked mole rat (*Heterocephalus glaber*) is a mouse-size rodent, but it lives ten times longer than mouse and is resistant to multiple age-related diseases, most notably cancer. Traditionally, molecular biologists focused their work on short-lived organisms, such as mice and rats, which reproduce and die rapidly, making them convenient genetic models. Although major aspects of genetics and physiology are conserved among mammals, short-lived species lack adaptations that confer long life. Since the ultimate goal of biomedical research is to prevent disease and extend lifespan, investigating mechanisms that confer longevity and disease resistance in long-lived species has tremendous potential. The discovery of high-molecular-mass hyaluronan that provides cancer resistance to naked mole rats exemplifies how studying a nonstandard species leads to a clinically relevant molecule.

Switching to nonstandard models may seem challenging, but it is also extremely rewarding as there is so much novel biology to be unearthed. The tools from whole-genome sequencing to RNAi and CRISPR/Cas9 technologies to study these atypical organisms are rapidly improving. The naked mole rat is just one example of a mammal that evolutionarily adapted to a long and healthy life. Many other long-lived species that have evolved unique mechanisms to stall aging and prevent disease such as beaver, gray squirrel, blind mole rat, Brandt’s bat, and bowhead whale await future investigation.

Ancient Immunity

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Jawed vertebrates ranging from sharks to humans mount adaptive immune responses using antigen receptors of the immunoglobulin superfamily. In contrast, the antigen receptors known as variable lymphocyte receptors (VLRs) in jawless vertebrates such as lampreys and hagfish generate diversity comparable to that of T cell and B cell receptors by assembling multiple leucine-rich repeat modules. This highlights the striking difference between the adaptive immune systems of jawed and jawless vertebrates and catapults lampreys and hagfish into the limelight in the immunology field. Interestingly, like jawed vertebrates, lampreys have three lineages of lymphocytes: one lineage of B-like lymphocytes and two lineages of T-like lymphocytes resembling $\alpha\beta$ and $\gamma\delta$ T cells, respectively. Therefore, it appears that specialized lymphocyte lineages emerged in a common vertebrate ancestor and that jawed and jawless vertebrates evolutionarily co-opted different antigen receptors within the context of such lymphocyte lineages.

Many questions remain unanswered. Do lampreys have antigen-presenting molecules with functions equivalent to those of major histocompatibility complex molecules? What is the chemical nature of ligands recognized by VLRs expressed on $\alpha\beta$ T-like lymphocytes? Do they recognize peptides like their gnathostome counterparts? How do lamprey lymphocytes undergo selection during their development in central lymphoid organs? Investigation of the immune system of these ancient jawless fishes will yield many more surprises and keep inspiring us for years to come.

Hive's Logic of Life

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Honey bees (*Apis mellifera*) provide remarkable opportunities for understanding complex behavior, with systems of division of labor, communication, decision making, and social aging/immunity. They teach us how social behaviors develop from solitary behavioral modules, with only minor "tweaking" of molecular networks. They help us unravel the fundamental properties of learning, memory, and symbolic language. They reveal the dynamics of collective decision making and how social plasticity can change epigenetic brain programming or reverse brain aging. They show us the mechanistic basis of trans-generational immune priming in invertebrates, perhaps facilitating the first vaccines for insects.

These processes and more can be studied across the levels of biological complexity—from genes to societies and over multiple timescales—from action potential to evolutionary. As models in neuroscience and animal behavior, honey bees have batteries of established research tools for brain/behavioral patterns, sensory perception, and cognition. Genome sequence, molecular tools, and a number of functional genomic tools are also available. With a relatively large-sized body ($\sim$1.5 cm) and brain ($\sim$1 mm^3), this fascinating animal is, additionally, easy to work with for students of all ages.

Beekeeping practices date as early as the Minoan Civilization, where the bee symbolized a Mother Goddess. Today, we increasingly value honey bees as essential pollinators of commercial crops and for their ecosystem services. Honey bees have been called keepers of the logic of life. They are truly.

Natural Neuroscience

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Through a reductionist approach, we made great progress in brain research by focusing on simple sensory stimuli and simplified, highly controlled laboratory behaviors. However, this reductionism came at a cost: it neglected what real brains evolved for—guiding behavior in real-world, complex natural environments. We know surprisingly little about natural behaviors of mice and rats—a fundamental gap in our understanding of brain and behavior in these "standard mammalian models." It is therefore crucial to study the neural basis of behavior under real-life, naturalistic conditions: a "Natural Neuroscience" approach.

One way would be to study wild rodents outdoors and then implement more naturalistic experiments indoors. Another way is to use "atypical" mammalian models, such as bats. Why bats? First, much is known about bats' natural behaviors in the field; in fact, the same species (and even same individuals) can be studied both outdoors and in the lab. Second, their 3D flight behaviors and long-distance navigational skills make bats excellent models for studying the neural basis of navigation. Third, bat sensory inputs (biosonar) can be recorded with sub-millisecond precision, making them great models for "active sensing." Finally, studying bats allows a "sanity check" of a key hidden assumption in modern biology—that all mammals are alike, from mouse to human. Comparative studies of bat and rodent brains—e.g., the role of hippocampal oscillations—have begun to argue against that assumption. This highlights the importance of studying circuits, networks, and neural codes across species.

Monkey Mind: A Memoir of Aging

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The lack of successful translation of findings from Alzheimer's disease rodent models to clinical trials has sparked interest in finding better animal models. Although studying large non-human primates such as macaques and Caribbean vervets has revealed important insights, their long life expectancy (up to 30 years in captivity) is a major drawback for longitudinal aging studies. Circumventing this problem, the short-lived gray mouse lemur (*Microcebus murinus*) has been developed as an alterative primate model for studying cerebral aging and Alzheimer's disease. Aged mouse lemurs (>6 years) show many human aging conditions, including cataracts, loss of olfactory acuity, reduced fine motor skills, and cognitive deficits. In addition, about 5%–10% of aged mouse lemurs develop abnormal behaviors indicative of "pathologic aging" such as aggressiveness, loss of social contact, and loss of biorhythm. Intriguingly, other pathological alterations, including massive brain atrophy, loss of cholinergic neurons, β-amyloid accumulation, and Tau aggregation, are similar to those associated with patients of Alzheimer's disease.

Features of mouse lemurs, such as small size (60–120 g), short lifespan (8–12 years in captivity), high fecundity (2–4 offspring per year), and early sexual maturity (10 months), make them more advantageous and suitable for genetic manipulations using CRISPR genome-editing technology. There are several laboratory-raised colonies around the world that would facilitate the expansion of this model for aging research.

A Fish in the Fountain of Youth

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The African turquoise killifish (*Nothobranchius furzeri*) is a fascinating organism. It lives in Zimbabwe and Mozambique in ponds that are only present during the brief rainy season and has evolved a naturally compressed lifespan adapted to this unusual habitat. The African killifish is an attractive new model to study aging and age-dependent diseases in vertebrates. Aging studies have long benefited from invertebrate models, such as worms and flies. But those organisms lack organs or systems, including bones, blood, and adaptive immune system, that are involved in age-related diseases. On the other hand, vertebrate models—mice and zebrafish—are limited by their longer life (2.5 and 4–5 years, respectively).

In developing new model organisms, it is important to consider what unique aspect they bring. The African killifish provides a natural short lifespan (4–6 months in optimal laboratory conditions) and recapitulation of age-dependent phenotypes and pathologies, including cognitive decline, sarcopenia, and cancerous lesions. It also replicates certain aspects of human biology better than current models. For example, its telomeres are comparable in size to those of humans. These characteristics, coupled with the ease of generating many offspring and low maintenance costs, make the African killifish a promising alternative vertebrate model for genetic and drug screening. The recent development of a genome-editing pipeline in this fish has the potential to transform how we explore aging and disease-related genes. The African killifish could also provide novel insight into the differences in lifespan strategies between species.

Vocal Learning

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Speech and language are central to the human experience, commanding extensive study in the realm of learning and memory. Songbirds have emerged as a powerful model for analogous animal research, informed by and informing the work in humans. Research in songbirds has identified how individual variation in vocal behavior arises from genetic and epigenetic factors. This includes not just the well-known zebra finch (*Taeniopygia guttata*) but also birds of all stripes, with extensive species-level variation in learned behavior representing a unique opportunity for study in the animal kingdom.

Combining the study of brain and learned behavior is also a powerful approach for addressing many questions of general interest to neurobiology. Songbird research is providing insight into systems-level questions such as how auditory memories are initially established, are consolidated, and influence motor output; computational questions such as how motor commands relate to movements and how a common time frame is maintained given that motor command, muscle activation, and sensory feedback progressively lag in time; and in-depth analysis of how network properties emerge from the interactions of single cells— influenced by a rich soup of transmitters and modulators; and a great many others. Recently, the zebra finch genome has been sequenced. Coupled with molecular and genomic approaches that are being adopted, this is providing for additional elegant experimental designs possible with songbirds. The sky is indeed the limit, and the future is melodious for this attractive model system.